to the theory that *H. influenzae* is responsible for the acute infective episodes which occur.

The need for further study of *H. influenzae* antigens is stressed.

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ACCIDENTAL INJECTION OF THIOPENTONE INTO ARTERIES

STUDIES OF PATHOLOGY AND TREATMENT

BY

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AND

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Thiopentone solution is sometimes injected accidentally into an artery in mistake for a vein during induction of anaesthesia. The clinical effects are well known. They range from gangrene and ischaemic contracture of muscles in the severe cases to minor degrees of anaesthesia of digits in the more fortunate patients. The clinical effects have been thoroughly described by Cohen in 1948, and by others whose publications are listed in the Bibliography. Uncertainty has existed about the nature of the vascular changes which follow the injection and which lead to the ischaemic end-results. This uncertainty has in turn led to some doubt on what treatment should be undertaken once the accident has happened.

Various factors have been suggested to explain the pathology. Prolonged arterial spasm has been postulated. It has also been suggested that the intimal layer of the artery is damaged and that thrombosis follows. The extreme alkalinity of thiopentone solution (usually about *p*H 10.9) has been blamed for these things. Widely differing treatments based on the uncertain nature of the pathology have been advocated or attempted. They have included the following measures:

(1) Injection into the damaged artery of a vasodilator drug. It has been advised that this be done immediately the accident has been discovered and, if possible, through the same needle without removing it. (2) The use of sympathetic or brachial-plexus block with local analgesic solution such as procaine (these measures being intended to relieve a postulated spasm of the injured artery). (3) Administration of anticoagulant drugs to prevent arterial thrombosis. (4) Arteriotomy and removal of clot from the vessel. (5) Arteriectomy: excision of a portion of the damaged vessel to relieve a theoretical reflex spasm of collateral branches.

Variable degrees of success have been reported after these measures, and it has been difficult to judge their efficacy under clinical conditions.

Laboratory Experiments

Investigations of the circulatory changes after intra-arterial thiopentone injections were for obvious reasons impossible in human subjects, so studies were undertaken in animals. The question of spasm was first investigated, employing a method similar to that described and used by Kinmonth and others in 1949, 1952, and 1957 in the rabbit and other animals. The intra-arterial injections were made into the femoral artery through a fine needle inserted just below the inguinal ligament. The needle-point was directed in a proximal direction as it would be under the clinical conditions of an accidental intra-arterial injection, and the needle was connected by a length of fine polyethylene tubing to a syringe to eliminate artifacts due to movement of the needle during injection. The artery was observed through a dissecting microscope a short distance below the site of injection, and changes in its diameter were measured with a micrometer eyepiece. Typical findings after an injection of 5% thiopentone are shown in Fig. 1.

There is a contraction of the vessel lasting about 30 seconds immediately after the injection of thiopentone. It is followed by a rapid return to the original diameter, after which a slight dilatation occurs for approximately one minute. On no occasion was any prolonged contraction observed nor anything at all resembling the spasm which follows mechanical trauma to an artery. Injections of buffered solution of alkalinity equal to that of thiopentone (0.1 M sodium carbonate/0.1 N hydrochloric acid, giving *p*H 10.9) produced no changes in the arterial diameter. This experiment was repeated many times with consistent results. On no occasion was anything other than transient contraction produced by thiopentone solutions, and alkaline solutions of equal *p*H never produced any change in arterial diameter.

The nature of the short-lived constriction and the ensuing vasodilatation after the thiopentone injection are of interest. They were also observed in animals where the femoral nerve had been divided and the femoral artery dissected free for a distance with the

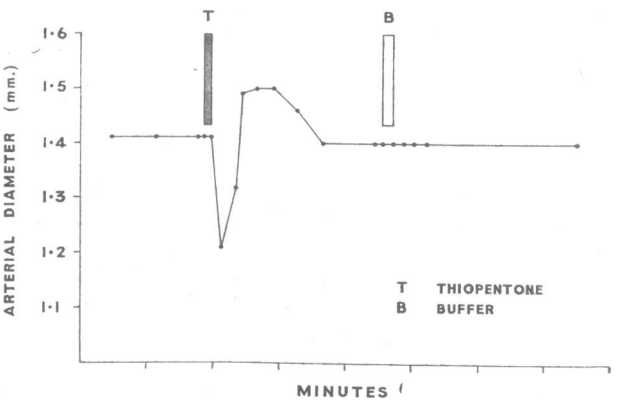

FIG. 1.—Injections into femoral artery of rabbits of (*a*) 0.5 ml. of 5% thiopentone at T, and (*b*) 0.3 ml. buffer solution of equal alkalinity (*p*H 10.9) at B.

object of denervating it. This suggests they were due to the direct effect of thiopentone on the vessel and not to a nervous reflex.

The period of vasoconstriction produced by the thiopentone injection is so short that it could not possibly explain the occurrence of necrosis after such an injection. Complete arrest of the circulation in the part by a tourniquet for much longer periods does not produce necrosis. Some cause other than vasoconstriction must be postulated to explain the occurrence of necrosis. That this might be so was also suggested by some experiments in which "ethamoline" (Glaxo) (Ethanolamine oleate *B.P.*) was injected into the femoral artery of the rabbit. No changes in diameter occurred after ethamoline injections, although thiopentone injections produced the same changes as those described above. Ethamoline is a substance regularly used to produce venous thrombosis in man, and can also be shown very readily to produce necrosis after intra-arterial injection in animals.

Production of Gangrene by Thiopentone Injection

The next step was to devise a method of intra-arterial injection of thiopentone in an experimental animal so that necrosis might be produced in such a way that it could be measured. The effects of countermeasures might then be tried, to see if the amount of necrosis could be reduced by treatment. After trials in different animals and at different anatomical sites it was found that injection into the central artery of the pinna of the rabbit fulfilled the requirements.

Technique

The rabbit was anaesthetized with intravenous pentobarbitone solution (26 mg./kg.). A light intestinal clamp was placed across the base of the pinna and a short incision made through the skin to expose the central artery, which was then injected retrogradely over a period of two minutes with thiopentone solution. The skin was closed with a few five-zero silk stitches. The clamp was used to stop bleeding around the artery and to facilitate the injection. It was also used to enhance the effect of the thiopentone, the dosage of which was limited because it was necessary to have the animal anaesthetized before the intra-arterial injection. It was found that an injection of 0.2 ml. of 10% thiopentone solution consistently produced massive gangrene of the pinna using this technique and keeping the clamp on the pinna for 15 minutes after the injection. This dose is roughly equivalent to an injection of 10 ml. of 10% thiopentone solution in a patient. Application of the clamp by itself for equivalent periods, or using this technique but injecting buffer solutions of equal alkalinity to the thiopentone, never produced any deleterious effects in the pinna.

The area of gangrene produced after three weeks by the standard technique just described is shown in Fig. 2. Some contraction usually occurred in and around the necrotic area, and so it was found that the area of tissue loss could be more accurately assessed at a later date, after the gangrenous area had separated, by measuring it in comparison with the contralateral control ear. The amount of tissue loss in another animal four weeks after injection is shown in Fig. 3. The average area of full-thickness loss of pinna was 14.5 sq. cm. in a series of 20 animals.

Effects of Countermeasures

Measures which might have been advocated as a form of treatment or which we thought might reduce the amount of tissue loss after intra-arterial thiopentone injection were next tried. They included intra-arterial injections of procaine solution, sympathetic denervation, and anticoagulant therapy with heparin.

1. Intra-arterial Injection of Procaine

Direct observation and measurement of the femoral artery of the rabbit by the method described above

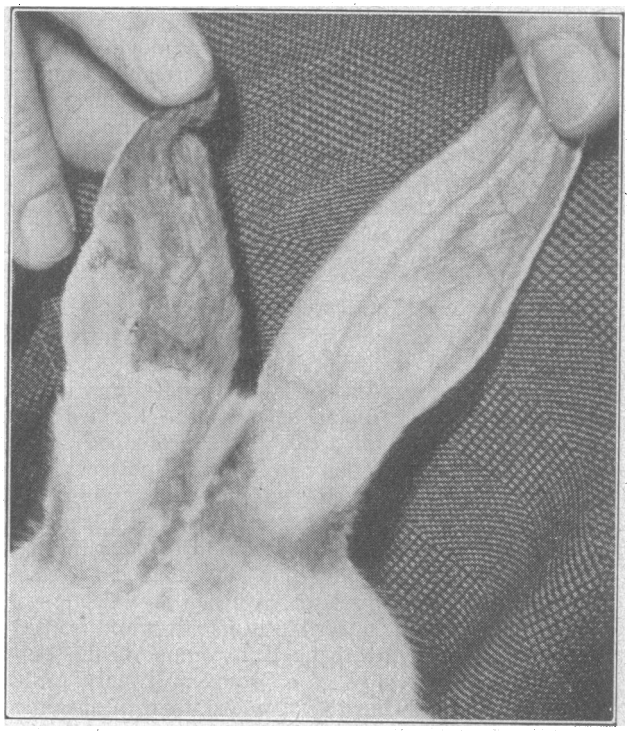

FIG. 2.—Showing area of gangrene produced by standard technique after three weeks.

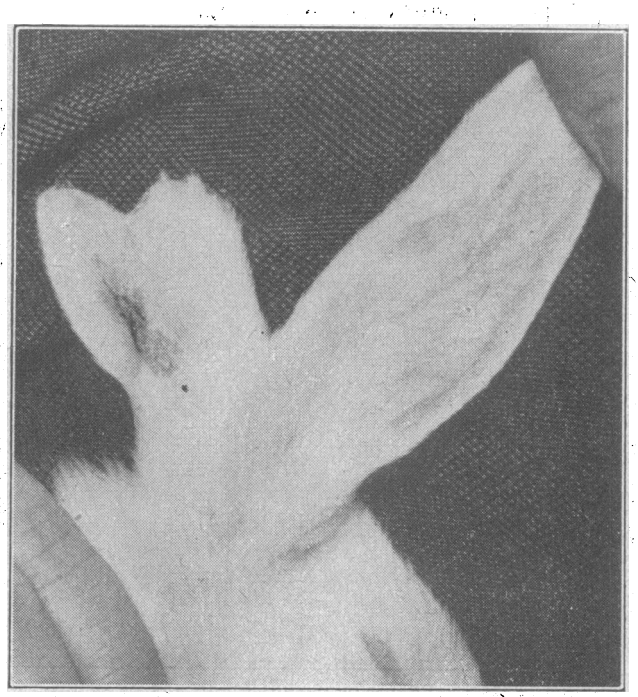

FIG. 3.—Tissue loss in another animal four weeks after injection.

showed that it was difficult to produce a prolonged vasodilatation of the artery by injecting dilator drugs such as procaine, tolazoline hydrochloride, or papaverine. The dilatation produced was invariably a transient one lasting no longer than five to ten minutes. Injection of procaine solution into an artery that has had thiopentone accidentally injected is, however, one of the main countermeasures advocated in clinical practice, and so it was decided to test whether it might have any protective effect after injection of thiopentone in the pinna of the rabbit. The thiopentone was injected with the standard technique described above. Procaine, 0.25 ml. of 4% solution, was then injected through the same needle and without removing it. The clamp was left upon the ear for the usual 15 minutes. This dose of 4% procaine is equivalent to some 5 to 10 ml. in a human patient. A series of 20 rabbits underwent this procedure. The average of the areas of tissue loss amounted to 15.2 sq. cm., which was approximately the same as that found in the untreated group, indicating that the procaine injections had no therapeutic effect.

2. Sympathetic Denervation

Removal of sympathetic vasomotor tone from the blood-vessels of the injured part is often advised as treatment for accidental intra-arterial injection of thiopentone. This might be supposed to give some protection by relief of a postulated prolonged arterial spasm. Our observations had failed to substantiate the occurrence of such a spasm, but sympathetic denervation might also be expected to exert a protective effect by increasing the flow of blood through the part, thereby discouraging clotting in damaged vessels. Blocking the vasoconstrictor pathways by injections of anaesthetic agents is uncertain in its effect and transient in duration, so sympathetic denervation of the pinna was effected surgically in a group of twenty rabbits immediately following the standard thiopentone injections. We are indebted to Dr. R. T. Grant of Guy's Hospital for advice on the method of doing this in the rabbit. The superior cervical ganglion and upper 1 in. (2.5 cm.) of chain was removed through an anterior incision. A short incision was then made behind the base of the pinna overlying the transverse process of the atlas, and the great and posterior auricular nerves were found and severed. Measurement of the tissue loss after the usual time showed it to be quite definitely less than in the untreated group, averaging 8.8 compared with 14.5 sq. cm. A typical example of an ear treated by this method is shown in Fig. 4.

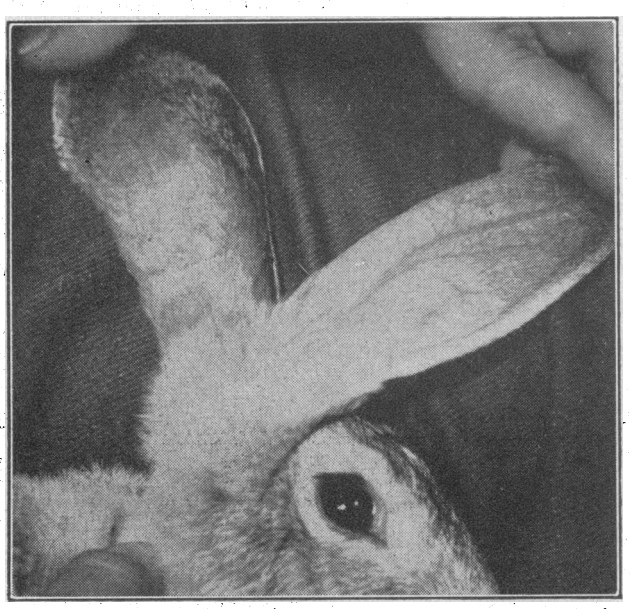

FIG. 4. Typical example of rabbit's ear treated by sympathetic denervation.

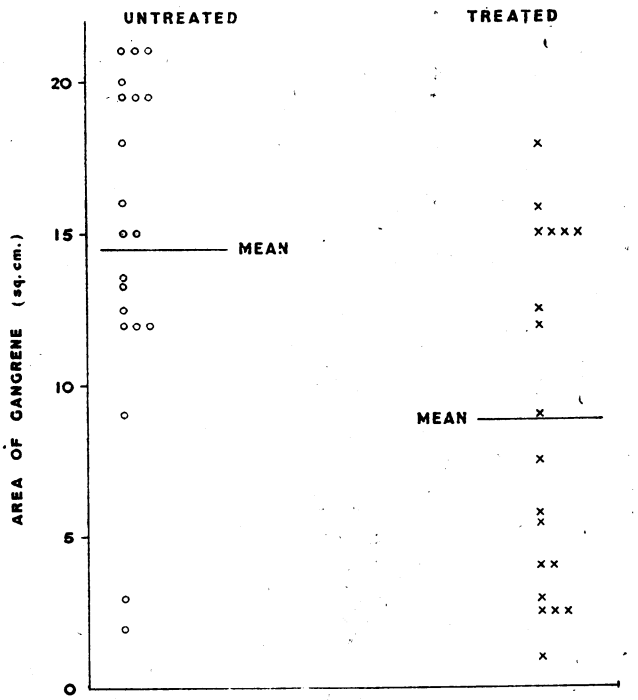

FIG. 5.—Effect of sympathectomy on area of tissue loss in pinna of rabbit after injection of thiopentone. Untreated animals on left had mean area of tissue loss of 14.5 sq. cm., animals treated by sympathectomy had mean tissue loss of 8.8 sq. cm.

There was a fairly wide scatter or variation in the area of gangrene which occurred in individual animals in both the treated and untreated groups, as may be seen in Fig. 5, but despite this there is a highly significant statistical difference.

3. Anticoagulant Therapy

The use of anticoagulant drugs might be expected to protect against ischaemic effects after intra-arterial injections of thiopentone by preventing thrombosis in the damaged vessels. The coumarol group of drugs were tried first, but were found to be difficult to administer and highly toxic in rabbits, and their use was not continued. Heparin was used instead, being given by intramuscular injection of 2,500 units/kg. every eight hours. Preliminary experiments showed that this high dosage was necessary in order to achieve a prolongation of the clotting-time of at least twice normal, lasting for seven to eight hours. A number of animals were lost from haemorrhage, usually at the site of intramuscular injection, but experience subsequently showed that it was necessary to maintain a high dosage for several days in order to produce a protective effect. In Table I the results are compared in a group of 15 animals in which full heparinization was effected for four days after intra-arterial thiopentone, compared with another group of 12 animals in which it was effected for only two days. The average areas of gangrene are 7.8 compared with 11.7 sq. cm.

TABLE I.—*Intra-arterial Thiopentone*

No. of Rabbits	Days of Full Heparinization	Av. Area Gangrene (sq. cm.)
15	4	7·8
12	2	11·7

TABLE II.—*Intra-arterial Thiopentone. Effect of Treatment*

Group	No. of Rabbits	Av. Area Gangrene (sq. cm.)
Untreated	20	14·5
Intra-arterial procaine ..	20	15·2
Sympathectomy	20	8·8
Heparin	30	9·2

The average area of tissue loss in 30 animals having full heparinization for two to four days after thiopentone amounted to 9.2 sq. cm. (see Table II). The first dose of heparin was injected into the central artery of the pinna immediately after removal of the clamp, subsequent doses being given intramuscularly every eight hours.

The protective effect compares well with that secured by sympathectomy but the mortality rate and practical difficulties in maintaining the treatment at an effective level were much greater.

Comparison of Different Protective Measures

The average areas of gangrene in four groups of animals in which the standard intra-arterial thiopentone injection had been made in the central artery of the pinna are shown in Table II. Intra-arterial procaine injections produced no effect, whereas both sympathetic denervation and heparinization had a definite protective effect and reduced the amount of gangrene after the thiopentone injections.

Prophylaxis

There is one possible prophylactic measure (other than the accepted methods of avoiding injection of an artery) which is subject to dispute and which is amenable to experimental test. This is the use of more dilute solutions of thiopentone for injection. The standard technique of intra-arterial injection was carried out in different groups of animals, varying the concentration of the thiopentone solution but using the same weight of drug. The results are shown in Table III.

The average area of gangrene proved to be inversely proportional to the strength of the solution of thiopentone used. When 2.5% solution was used for the injection the incidence of tissue loss was very low indeed. This relation of concentration to the extent of the necrosis ensuing was borne out by a review of published accounts of clinical cases (Table IV).

The numbers in each group are small, but they support the belief that the more dilute solutions are safer.

TABLE III.—*Intra-arterial Thiopentone. Effect of Varying Concentration*

Concentration of Thiopentone	No. of Rabbits	Average Area of Gangrene (sq. cm.)
10%	20	14·8
5%	10	10·4
2½%	10	0·15

TABLE IV.—*Intra-arterial Thiopentone. Incidence of Gangrene in Reported Cases*

Concentration of Thiopentone Used	No. of Cases	Cases with Gangrene
10%	10	6
5%	18	2
2½%	4	0
Unknown	2	0

Discussion

The sequence of events in an artery after an injection of thiopentone seems to be a momentary contraction followed by a short dilatation and return to the previous diameter. No prolonged spasm was observed in any artery. Later oedema and often redness and signs of inflammation develop in the affected part. This lasts for a variable time before occlusion of the circulation in the part occurs and it becomes cold. It was not possible to time the latter event in all animals, but it sometimes occurred as late as the third or fourth day. That the occlusion was due to thrombosis of the damaged artery was supported by evidence obtained from section and microscopy of the parts, but this evidence is not complete, as only a small number of animals were examined in this way, the majority being kept for assessment of the area of tissue loss.

Preservation of the injured tissues depends on maintaining the blood-flow through the part until recovery takes place. This may be done equally well by maintaining a brisk blood-flow by means of sympathectomy or by the use of heparin to prevent vascular thrombosis. Should heparin be used it might be wise to maintain the use of the drug for at least a week in view of reported clinical cases where the onset of ischaemia was delayed.

In a clinical case where thiopentone has been injected into an artery during induction of anaesthesia it would seem best to avoid going on with the intended operation and to place the patient on intensive heparin therapy. Should postponement of the operation be dangerous, then neurectomy of the sympathetic supply to the affected limb should be performed surgically.

Conclusions

There is no evidence that prolonged arterial spasm is the cause of the ischaemia following intra-arterial injection of thiopentone.

The ischaemia is caused by vascular occlusion due to damage by the thiopentone.

The injury is caused by the thiopentone itself and not by its alkalinity.

Sympathectomy or heparinization diminishes the ischaemic effects of injection.

Intra-arterial injections of vasodilator drugs are ineffective.

The danger of ischaemic changes after an intra-arterial injection is greater with strong than with dilute solutions of thiopentone.

We are grateful to Mr. M. P. Curwen, of St. Bartholomew's Hospital, for his help with statistical aspects of this work. Mr. S. M. Cohen has made freely available his considerable data on clinical aspects of the problem. Professor L. Young kindly supplied the buffered alkaline solutions. Mr. F. Scholefield and Miss N. Lowater have given technical assistance.

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GANGRENE OF FOREARM AFTER INTRAMUSCULAR CHLORPROMAZINE

BY

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Anaesthetists are aware of the catastrophes associated after the spread of accidental extravenous injection of piridoosal-diethazine (Sénèque and Huguenard, 1953), 1955). Recently, similar tragedies have been reported with hydroxydione (Schwarzkopf, 1958), and also after the spread of accidental extravenous injection of piridosal-diethazine (Sénèque and Huguenard, 1953), and promazine (Opinsky *et al.*, 1958). Gangrene due to an intramuscular premedicant injection is a less-known hazard, and appears to have been unreported.

Case Report

A woman aged 52, with a history of constitutional psychotic instability, accidentally sustained severe third-degree burns covering approximately 35% of her total body surface from the waist downwards.

After skin-grafting, the patient relapsed into acute mania, which made treatment difficult. During psychotherapeutic therapy the burnt areas were treated in enveloping plaster and were re-dressed as necessary under light general anaesthesia. Sepsis and decubitus ulceration took place under the plaster jacket, resulting in toxaemia and signs of renal damage. Blood transfusions and strenuous general measures were continuously necessary to maintain her general condition. After five months of treatment the patient had improved mentally and was alert and sensible, but her physical state had slowly depreciated and she had not tolerated repeated anaesthesia well. The dressings were latterly performed under light basal sedation. On the second occasion 50 mg. of chlorpromazine was ordered by intramuscular injection. The patient's legs and buttocks were covered with healing burns, and previous intravenous and intramuscular therapy had left residual soreness in both arms.

The injection (2 ml. of 2.5% solution), which was administered by a trained staff nurse, was given into the anterior aspect of the right biceps area, this being considered to be the best available site. No complaint of pain or discomfort was made by the patient at the time of injection, but twenty minutes later she remarked that her arm felt dead. On examination the arm was found to be flaccid, cold, and white. The brachial artery was pulsating in the upper arm, but from the site of injection downwards no circulation could be detected. From 1½ in. (3.8 cm.) above the elbow-joint to the finger-tips the limb appeared to be completely exsanguinated. Procaine (5%) was immediately infiltrated around the brachial artery at the injection level, and 25 mg. of tolazoline was administered intramuscularly. Neither measure had any obvious effect. Two and a half hours later a stellate ganglion and brachial plexus block was performed, using 1% lignocaine; this was followed after 15 minutes by Horner's syndrome, but by no alteration in the appearance of the arm. A few minutes later 40 mg. of papaverine in 20 ml. of water was injected into the subclavian artery, after which there appeared to be a slight flushing of the skin for an inch (2.5 cm.) or more below the previous line of exsanguination. Immediately after this procedure an intravenous injection of 15,000 units of heparin was given. Surgical exploration was undertaken eight hours from the time of the original intramuscular injection, the patient receiving light general anaesthesia with thiopentone, cyclopropane, nitrous oxide, and oxygen. The brachial artery, exposed in the upper arm, was found to be pulsating and healthy. At the level of the intramuscular injection there was some periarterial discoloration and haematoma formation, but no evidence that the artery had been punctured. From here downwards the vessel was contracted and immobile, and no blood could be aspirated therefrom. A 2% solution of papaverine was applied locally and 40 mg. of the drug in 20 ml. of water was injected into the artery at its lowermost normal point. These measures had no visible effect. Arteriotomy and arteriectomy were considered inadvisable.

Post-operatively, continuous heparinization was maintained and vasodilatation was encouraged by intramuscular tolazoline and by contralateral limb-heating. Support and gentle passive exercises were applied to the affected limb. In a few days there was a slight regression of the exsanguinated area on the radial side of the arm, and mottled bluish patches appeared around the surgical wound in the upper arm and spread into the forearm, particularly on the ventral aspect. The remainder of the forearm and hand remained bloodless, flaccid, and cold. Dry mummification took place in the finger-tips (Figs. 1 and 2). A line of separation eventually appeared, medially just below and laterally just above the elbow-joint. By the fifth day it was obvious that amputation of the forearm was inevitable, but in view of the patient's gradually depreciating condition conservative treatment was continued. The

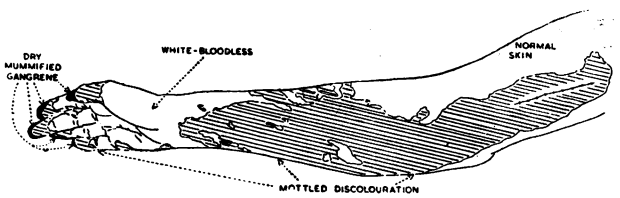

FIG. 1.—Ventral aspect of arm eight days after an intramuscular injection of chlorpromazine.

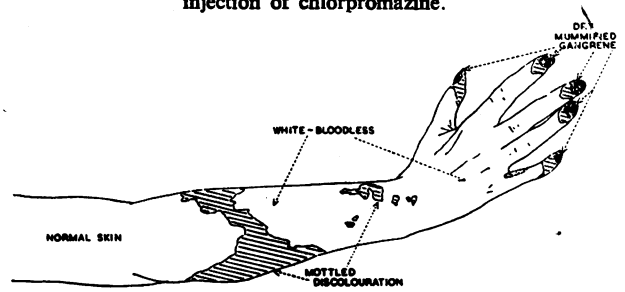

FIG. 2.—Dorsal aspect of arm eight days after an intramuscular injection of chlorpromazine.